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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,892	02/27/2002	Shukti Chakravarti	021825-004720US	1524

20350 7590 11/15/2006

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,892	CHAKRAVARTI, SHUKTI	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16-18,27,28 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 14, 15, 19-26, 29 and 30 have been canceled as filed on 8/31/06;

Claims 1-13, 16-18, 27, 28 and 31-36 are currently pending;

Claims 1-13 and 16-18 have been withdrawn;

Claims 27, 28 and 31-36 are being examined in this application.

Election/Restrictions

2. Applicant's election of Claims 27-36 in the Reply filed on 1/13/2006 is as previously acknowledged.

Priority

3. This application is a CIP of 09/694,758 (filed on 10/23/2000), which claims priority to provisional applications 60/160,835 (filed on 10/21/1999).

Rejections Withdrawn

4. In light of the amendments to the claims, the following rejections under 35 U.S.C. 102(e) an 103 (a) as set forth in the previous office action are withdrawn:

1.) Claims 27-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998).

2.) Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Dieckgraefe et al (Gastroenterology, vol. 114, no. 4, G3954; April, 1998; cited previously; IDS 8/12/2002), in view of Nielsen et al (Gut, Vol. 38: 414-420; 1996).

3.) Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Dieckgraefe et al (Gastroenterology, vol. 114, no. 4, G3954), in view of Cocks et al (US 6,607,879; 2003; filed 2/9/1998).

4.) Claims 27-36 are rejected under 35 U.S.C. 103(a) as being obvious over Heller et al (Proc. Natl. Acad. Sci. USA. Vol. 94, pages 2150-2155, March 1997; cited previously), in view of Cocks et al (US 6,607,879; 2003; filed 2/9/1998).

However, new rejections are written over the previously cited references (Cocks, Dieckgraefe, and Nielsen) as set forth below in the "New Rejections Necessitated by Amendment" section. Applicants' relevant traversal over the previously cited references are addressed in the same section in the instant Office action.

5. In light of the amendments to the claims, the following rejections as set forth in the previous office action are withdrawn:

1.) Claims 27-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

7. Claims 27, 28 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection over Claims 29 and 30 is moot due to applicant's cancellation of the said claims.

The instant claims are drawn to an array comprising nucleic acid probes for determining gene expression levels of at least of the listed specific genes. The said array has the intended use of diagnosing inflammatory bowel diseases by comparing different gene expression levels.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

Written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not case involves question of priority, since requirement applies to all inventions including chemical inventions, and since the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide description of compound sufficient to distinguish

infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

The instant specification and/or the aforementioned claims do not provide adequate written description to show possession of the entire genus of IBD. IBD encompasses a variety of diseases with different symptoms and clinical manifestations as taught by, for example, Robbins et al. (Pathologic Basis of Disease. 2nd ed., 1979. Page 958 and Page 982). The instant specification and/or claims do not provide an adequate number of representing species of the different diseases. It is not clear in the instant specification or claims that the claimed probes for the different genes can be used for monitoring gene expression in all inflammatory bowel diseases. For example, a specific gene might be overexpressed compared to the control sample in one type of IBD, but may be normally expressed in another type of IBD. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The instant claims are drawn to an array comprising various nucleic acid probes, which are used to determine the gene expression level of at least one gene in a sample. The instant specification defines the term Microarray as "an array of distinct polynucleotides or oligonucleotides synthesized on a substrate..." (para. [0070]), which is interpreted to mean that the DNA microarray contains nucleic acids with defined sequences. However, neither the instant specification nor the claims specifically recite nucleic acid probes that constitute the claimed array. Claim 27 recites an array comprising nucleic acid probes for determining an expression level of at least one gene from 4 listed genes (i.e. GRO3, HNL, elafin, and COL6A3). The said "nucleic acid probes" could be different DNA molecules such as cDNA of the claimed genes, or

short oligomers that are complementary to either the coding strand or the complement strand. The probes could also contain mutations relative to the wildtype gene sequences. The probes could even be complements to genes that regulate the said 4 genes. In addition, the probes could also have various lengths or sequence segment within the claimed gene sequence. These different variables together would create almost infinite combinations of different probes that could be encompassed by the claimed array of the probes. Furthermore, the instant specification and the claims only provide GenBank accession number for the claimed genes. The specific sequences for the probes that can hybridize to these genes are not provided. In addition, the GENBANK accession number do not provide a reference to a stable, know and non-changing source of information. GENBANK information may be updated and revised anytime (see http://www.ncbi.nih.gov/Genbank/index.html (2006) under the heading Updating or Revising a Sequence; cited previously), therefore, the sequence for the claimed genes could change anytime. One skilled in the art would not be able to envision that the applicants' had possession of the recited invention as described. It is unclear as to what portion(s) of the gene sequences are used, or suitable for the said probes for the array.

The Court of Appeals for the Federal Circuit, our reviewing court, has addressed the issue of what constitutes adequate written description for a claim drawn to a nucleic acid. In Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1602 (Fed. Cir. 2002), the court adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

> The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics.

Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613 (citations omitted).

The court also addressed the issue of what constitutes adequate written description of a claim to a broad genus of sequences. In The Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998), the court determined that the disclosure of rat cDNA did not provide adequate written description support for claims drawn to mammalian and vertebrate DNA. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. The court stated:

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.
> Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In Enzo-Biochem, the court refined the approach advanced by Eli Lilly, adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Thus, adequate written description may be present for a genus of nucleic acids based on their hybridization properties, "if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Enzo Biochem, 296 F.3d at 1327, 63 USPQ2d at 1615.

Here, Applicants fail to claim probes that hybridize under "stringent" conditions. Thus, the current claims encompass a myriad of probes that are not "structurally similar." This would include virtually an infinite number of possibilities. In contrast, Applicants' specification does not even disclose a single working example of a specific nucleic acid probe that can be used on

an array for detecting sample gene expression. This also would lead to a target that could potentially bind to numerous "low affinity" probes.

As discussed above, the skilled artisan cannot envision the nucleic acid probes that constitute the said array. Regardless of the complexity or simplicity of the method of creating such composition, adequate written description requires more than a mere statement that it is part of the invention and reference to a possibility of creating it. The composition itself is required.

Discussion and Answer to Argument

8. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue that IBD does not encompass a variety of diseases with different symptoms and clinical manifestations, and citing Robbins et al as evidence to support the assertion. (Reply filed 8/21/06, pp. 7-8).

Contrary to applicant's assertion, IBD does encompass a variety of diseases as indicated by Robbins et al (Pathologic Basis of Disease. 2nd ed., 1979. Page 958 and Page 982; cited previously). The reference provides a list of different diseases that are classified under IBD (e.g. the list of p. 958). Applicant's traversal is based on the argument that the major two IBD subtypes, Crohn's disease (CD) and ulcerative colitis (UC) have similar features. This is not persuasive, because CD and UC are only two types of IBD, and they do not constitute all possible types of diseases that are categorized under IBD.

The instant specification only provides a brief description of monitoring certain gene expressions using microarray (e.g. p. 12-17). The specification does not provide description of all the probes that can be used for the microarray, nor provide representative numbers of species of probes that can be used for the claimed purpose. Thus, instant specification does not provide adequate written description to show possession of all the probes that can be used for diagnosing all possible types of IBDs including UC and CD.

Applicants argue the instant specification "clearly demonstrates to one of skill in the art that the present invention was in full possession of the claimed invention at the time of filing". Applicants specifically argued the followings:

1.) The GenBank accession number does provide the specific sequence for each claimed gene.

2.) The specification provides structure and length for the nucleic acid probes such as "at least about 12-40 nucleotides in length" that is complementary to a portion of the coding sequence of a claimed gene.(Reply, p. 9, 3rd para).

3.)The instant specification provides binding specificity (hybridization conditions of low, medium or high stringency) of the nucleic acid. (Reply, pp. 9-10.)

To address applicant's first argument, the GenBank accession number does not provide a constant and unchanging source of specific sequence information for the claimed genes. For example, the Elafin gene is provided with the GenBank accession number, X52022 (Table 1 of the instant spec.). The GenBank accession number, X52022, has many revisions and different

versions of the sequences for the Elafin gene, as indicated by the "Revision History" (see Attached copy of the "Sequence Revision History" for X52022; downloaded 11/4/06). The sequence version updated on 4/21/1993 has a length of 9930 nucleotides (see attached GenBank printout #1; downloaded 11/4/06), but the sequence version updated on 3/9/1999 has a length of 10558 nucleotides (see attached GenBank printout #2; downloaded 11/4/06). In addition, a BLAST alignment does not show complete sequence identity between the two versions of sequences under the same GenBank accession number (see attached "Blast 2 Sequences Result"; downloaded 11/4/06).

Without knowing the specific nucleic acid sequences for a particular gene, the possession of the specific nucleic acid probes (whose sequences are dependent on the gene sequence) are also not known. Furthermore, the instant specification only provides ranges of probe lengths (e.g. 12-40 nucleotides), but not specific sequence information. As pointed out by applicants, written description for biomolecules may be shown through examples of identifying characteristics such as sequence (Reply, p. 9, 2nd para). A recitation of a probe of 12 nucleotides long out of 10558 nucleotides (of the Elafin gene), for example, does not provide specific structural limitation for the claimed probe.

Similarly, the property of binding specificity of a given probe also does not provide a structural limitation for the claimed probes. Without the specific sequence information, the binding specificity of a particular probe cannot be determined, and thus would not offer additional structural limitation. Applicants have pointed out the specification has described the nucleic acid probes in term of hybridization stringency including low, medium and high (Reply,

p. 9, bottom). First these different stringencies recited in the specification would encompass different probes, which may or may not share common structure.

In Enzo-Biochem, the court refined the approach advanced by Eli Lilly, adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Thus, adequate written description may be present for a genus of nucleic acids based on their hybridization properties, "if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Enzo Biochem, 296 F.3d at 1327, 63 USPQ2d at 1615.

Here, Applicants fail to claim probes that hybridize under "stringent" conditions. Thus, the current claims encompass a myriad of probes that are not "structurally similar." This would include virtually an infinite number of possibilities. In contrast, Applicants' specification does not even disclose a single working example of a specific nucleic acid probe that can be used on an array for detecting sample gene expression. This also would lead to a target that could potentially bind to numerous "low affinity" probes.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 27, 28 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998; cited previously), Nielsen et al (Gut, Vol. 38: 414-420; 1996; cited previously), and Sallenave et al (Biological Chemistry Hoppe-Seyler. Vol. 373: 27-33; 1/1992).

The instant claims as amended are drawn to an array for diagnosing inflammatory bowel disease (IBD) in a subject comprising:

(a) nucleic acid probes for determining an expression level of at least three genes in a sample from said subject, wherein said genes are selected from the group consisting of macrophage inflammatory protein-2β (GRO3), neutrophil lipocalin (HNL), elastase specific inhibitor (elafin), and type VI collagen α3 chain (COL6A3); and

(b) a substrate to which said nucleic acid probes are bound, wherein a difference in the expression level of each of said genes in said subject compared to an expression level of the same gene in a healthy tissue indicates that said subject has IBD or is at risk of developing IBD.

The claimed array has intended use of diagnosing inflammatory bowel disease by comparing the expression level of the listed genes.

Cocks et al teach a microarray comprising cDNAs with SEQ ID Nos: 1-1508 (See Claim 1 of the reference). The reference teaches the cDNAs (reads on nucleic acid probes that specifically hybridize to the gene product of **clm 33**) are immobilized on a substrate and are hybridizable elements on a microarray (Claims 2 and 3 of the reference), which reads on the microarray and its probes of **clm 27**. The reference also teaches that SEQ ID No 1100 is human cytokine (GRO-γ) (See Table 1 of the reference), which reads on **GRO3** of **clm 27**. The reference further teaches that the transcripts (mRNA) used with the array are obtained from various sources such as inflamed samples and noninflamed biological samples from various tissues such as hematopoietic tissues or colon tissues (Col. 7, 1st paragraph and lines 10-25), which would read on gene product from a tissue of **clm 32**. In addition, the reference teaches comparing the hybridization pattern from diseased and non-diseased samples (Claim 4), which would read on the intended use of the instant **clm 27**. The reference also teaches that the

immunopathological condition is Crohn's disease, and/or ulcerative colitis, which read on the UC of **clm 28**. The reference further teaches that transcript levels are preferably at least about 2xhigher in a diseased sample than in the nondiseased sample (Col. 7, lines 22-25), which reads on the intended use of **clm 31**. Furthermore, the reference teaches that the polynucleotide probes can be synthesized on the surface of the substrate by using n covalent bonding to the substrate (Col. 10, lines 20-22, for example), and the substrates used could be chips, membrane, plates, etc. (Col. 10, lines 1-5), which read on the covalent interaction of **clm 34,** 2D matrix of **clm 35,** the substrates of **clm 36**.

Cocks et al, do not specifically teach the microarray comprise probes for the other listed genes (such as HNL and elafin), as recited in **clm 27**.

However, Nielsen et al teach a neutrophil gelatinase associated lipocalin (reads on the **HNL** gene of **clm 27)** that over expressed in the epithelial cells in inflammatory bowel diseases (See Abstract of the reference). The reference also teaches that the synthesis (expression) of human neutrophil lipocalin is an important cellular response to inflammation in colon epithelium, and the faecal content of the protein may therefore prove to be a useful marker for disease activity in inflammatory bowel disease (See Page 419, right col. Last paragraph).

Sallenave et al, throughout the publication, teach **Elafin** and the specific sequences for its gene and protein (see p. 51, for example). The reference also teaches Elafin "is not of single origin but is probably a marker of inflammation ... presented in different tissues" (Abstract of the reference).

Therefore, it would have been prima facie obvious at the time the invention was made for a person of ordinary skill in the art to generate an array with nucleic acid probes that specifically hybridize with a particular gene (e.g. HNL and elafin).

A person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for the HNL gene, because Nielsen et al teach that the specific gene for the human neutrophil lipocalin (HNL) could be a marker for detecting IBD.

A person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for the Elafin gene, because Sallenave et al teach that the specific gene for the protein Elafin is correlated with inflammation that is associated with various diseases, and Elafin can be found in different tissues.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications since the method of generating a microarray with specific nucleic acid probes are know in the art such as the one taught by Cocks et al and the specific gene sequence for the desired marker is also know as taught by Nielsen et al and Sallenave et al.

11. Claims 27, 28 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol. 114, no. 4, G3954; April, 1998; cited previously; IDS 8/12/2002), Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998; cited previously), Nielsen et al (Gut, Vol. 38: 414-420; 1996; cited previously), and Sallenave et al (Biological Chemistry Hoppe-Seyler. Vol. 373: 27-33; 1/1992).

Dieckgraefe et al, throughout the publication, disclose characterization of mucosal gene expression in inflammatory bowel disease (IBD) by direct hybridization to massive parallel oligonucleotide arrays (see the entire document), which reads on the array of **clms 27** and **35.** The reference discloses that parallel or high throughput methods of measuring gene expression have been recently developed which allow concurrent measurement of the expression pattern of a large number of genes. The reference discloses the use of Gene chip (refers to the solid support chip and two dimensional matrix of the instant claims) expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohn's colitis to identify genotypes associated with particular disease. This reads on the intended use of **clms 27** and **28**. The reference discloses that RNA isolated from the mucosal colonial specimens was used to generate hybridization probes, which reads on the samples of **clm 32**. The reference further discloses that light directed solid phase (refers to the support of the instant claims of **clm 36**) combinatorial chemistry (would refer to covalent bonding of probes to the substrate of **clm 34**) was used to generate oligonucleotide probe arrays (refers to nucleic acid probes of the instant claim array) which provide representation of nearly 7000 human cDNA and EST sequences, which reads on the probes specifically hybridize to the gene products of **clm 33**. The reference also teaches the dramatic changes in gene expression were observed, which reads on the intended use of measuring the expression levels of **clm 31**. The reference further discloses that hybridization to the oligonucleotide arrays was sensitive, specific and reproducible.

Dieckgraefe et al do not specifically teach the specific genes listed in **clm 27** of the instant application.

However, Cocks et al teach a microarray comprising cDNAs with SEQ ID Nos: 1-1508 (See Claim 1 of the reference), which SEQ ID No 1100 is human cytokine (GRO-γ) (See Table 1 of the reference), and reads on **GRO3** of **clm 27**. The reference also teaches that the array is particular useful for diagnosing and monitoring particular diseases such as Crohn's disease (col. 14, lines 50+).

Nielsen et al teach a neutrophil gelatinase associated lipocalin (reads on the **HNL** gene of **clm 27)** that over expressed in the epithelial cells in inflammatory bowel diseases (See Abstract of the reference). The reference also teaches that the synthesis (expression) of human neutrophil lipocalin is an important cellular response to inflammation in colon epithelium, and the faecal content of the protein may therefore prove to be a useful marker for disease activity in inflammatory bowel disease (See Page 419, right col. Last paragraph). The reference also teaches (page 416, left col. 4th para.) affected tissues from ulcerative colitis and Crohn's disease showed strong NGAL expression whereas unaffected tissues were negative for NGAL expression, which reads on the intended use of detecting expression levels of gene products that differ by at least a factor of two, as recited in **clm 31**.

Sallenave et al, throughout the publication, teach **Elafin** and the specific sequences for its gene and protein (see p. 51, for example). The reference also teaches Elafin "is not of single origin but is probably a marker of inflammation ... presented in different tissues" (Abstract of the reference).

Therefore, it would have been prima facie obvious at the time the invention was made for a person of ordinary skill in the art to generate an array with nucleic acid probes that specifically hybridize with a particular gene (e.g. HNL, GRO3, and elafin).

A person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for the GRO3 gene, because Cocks et al teach that the specific gene for GRO3 as part of a microarray is particular useful for detecting IBDs such as Crohn's disease.

A person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for the HNL gene, because Nielsen et al teach that the specific gene for the human neutrophil lipocalin (HNL) could be a marker for detecting IBD.

A person of ordinary skill in the art would have been motivated at the time of the invention to design a microarray comprising probes for the Elafin gene, because Sallenave et al teach that the specific gene for the protein Elafin is a marker for inflammation that is associated with various diseases, and Elafin can be found in different tissues.

An ordinary skilled artisan would have reasonable expectation of success of achieving such modifications since the method of generating a microarray with specific nucleic acid probes are know in the art such as the ones taught by Dieckgraefe et al and Cocks et al, and the specific gene sequence for the desired marker is also know as taught by Nielsen et al and Sallenave et al.

Discussion and Answer to Argument

12. Applicant's relevant arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed over the Cocks, Nielsen, Dieckgraefe references with the same argument. Applicants argue that these references either alone or in combination does not teach

all elements of the amended claims, which requires probes for "at least three gene" listed in ***clm*** *27 to be on the claimed microarray.*

The new rejections necessitated by amendment using the above listed references are in combination with Sallenave et al, who teach Elafin (the third gene), and also provide motivation to combine with the Cocks, Nielsen, and Dieckgraefe references, as discussed in the rejections above.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 33** recites the limitation "said gene product" in the line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 33 and all dependent claims are rejected under 35 USC 112, second paragraph.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1639
11/6/2006

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